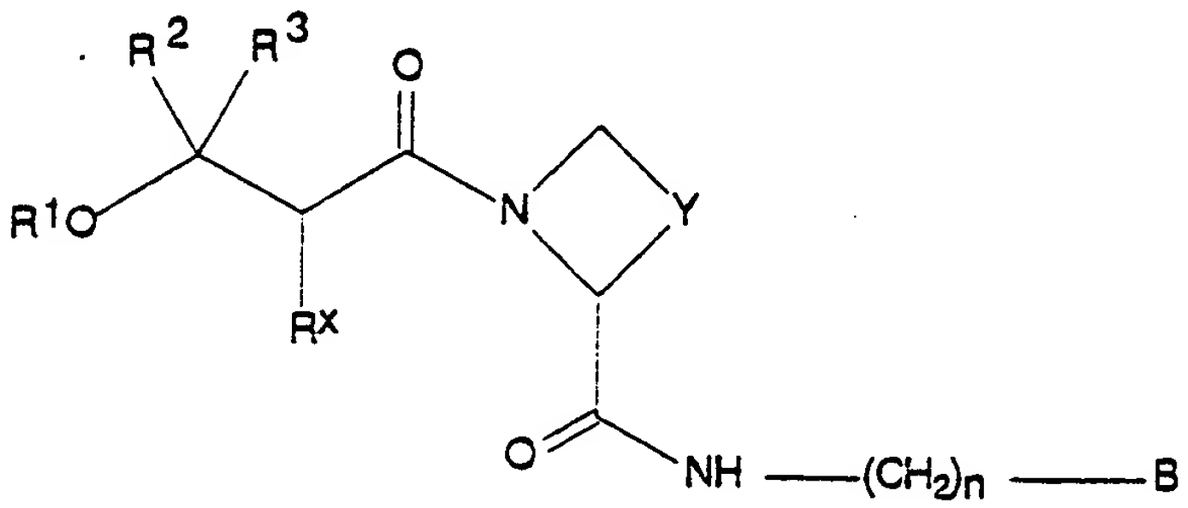
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 3 and 4 are canceled without prejudice.

1. (Three Times Amended) A compound of formula I,



wherein

R^1 represents H[, $C(O)R^{11}$, $SiR^{12}R^{13}R^{14}$ or C_{1-6} alkyl which latter group is optionally substituted or terminated by one or more substituent selected from the group consisting of OR^{15} and $(CH_2)_qR^{16}$];

R^{12}, R^{13} and R^{14} independently represent H, phenyl or C_{1-6} alkyl;

R^{16} represents C_{1-4} alkyl, phenyl, OH, $C(O)OR^{17}$ or $C(O)N(H)R^{18}$;

R^{18} represents H, C_{1-4} alkyl or $CH_2C(O)OR^{19}$;

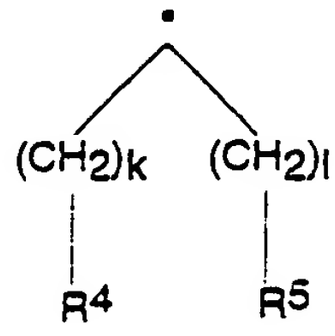
R^{15} and R^{17} independently represent H, C_{1-6} alkyl or C_{7-9} alkylphenyl;

R^{11} and R^{19} independently represent H or C_{1-4} alkyl; and

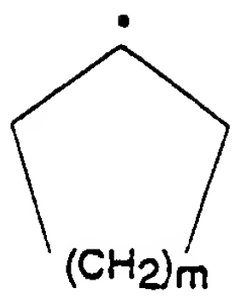
q represents 0, 1 or 2;

R^2 and R^3 are both hydrogen;

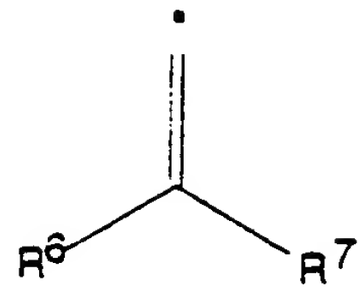
R^x represents a structural fragment of formula IIa, IIb or IIc,



IIa



IIb



IIc

wherein

k, l and m independently represent 0, 1, 2, 3 or 4;

R^4 and R^5 independently represent H, $Si(Me)_3$, 1- or 2-naphthyl, a polycyclic hydrocarbyl group, $CHR^{41}R^{42}$ or C_{1-4} alkyl (which latter group is optionally substituted by one or more fluorine atoms), or C_{3-8} cycloalkyl, phenyl, methylenedioxyphenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl (which latter twelve groups are optionally substituted by one or more of C_{1-4} alkyl (which latter group is optionally substituted by one or more halo substituent), C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, SO_2NH_2, C(O)OH or $N(H)R^{43}$);

R^{41} and R^{42} independently represent cyclohexyl or phenyl;

R^6 and R^7 independently represent H, C_{1-4} alkyl, C_{3-8} cycloalkyl, phenyl (which latter group is are optionally substituted by one or more of C_{1-4} alkyl (which latter group is optionally substituted by one or more halo substituent), C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, SO_2NH_2, C(O)OH or $N(H)R^{44}$) or together with the carbon atom to which

they are attached form a C_{3-8} cycloalkyl ring;

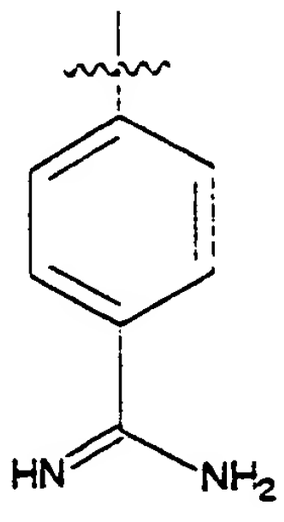
R^{43} and R^{44} independently represent H or $C(O)R^{45}$; and

R^{45} represents H, C_{1-4} alkyl or C_{1-4} alkoxy;

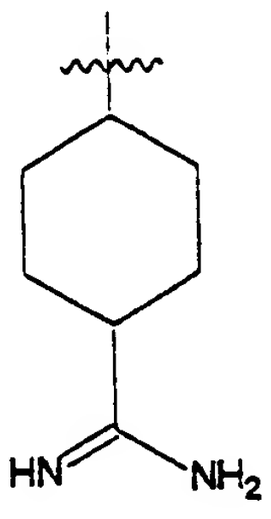
Y represents $(CH_2)_2$, CH=CH, $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$, which latter three groups are optionally substituted by C_{1-4} alkyl, methylene, oxo or hydroxy;

n represents 0, 1, 2, 3 or 4; and

B represents a structural fragment of formula IVa or IVc



IVa



IVc

or a pharmaceutically acceptable salt thereof.

10. (Twice Amended) A compound as claimed in claim 1 which is

(*R,S*)-PhCH(CH_2OH)-C(O)-Pro-(*R,S*)-Hig;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-aminophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(methylamino)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-(methylamino)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-PhCH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-((3-chloro-5-methylphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-((3-chloro-5-methylphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-fluorophenyl-CH(CH_2OH)CO-Pro-Pab;

(*R*)-3-fluorophenyl-CH(CH_2OH)CO-Pro-Pab;

(*S*)-3-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3,5-bis(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3,5-bis(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-methoxy-5-methylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-(2,5-dimethoxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-(3,5-dimethoxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,4-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-(2-naphthyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(2-naphthyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-2,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxy-4-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-methoxy-4-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3,5-dichlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3,5-dichlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-2,3-dimethoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2,3-dimethoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxy-5-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-methoxy-5-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-2-methyl-5-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2-methyl-5-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

[(*R,S*)-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab;]

(*R*)-2,3-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab; or

(*S*)-2,3-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab

or a pharmaceutically acceptable salt thereof.

19. (Twice Amended) A compound as claimed in claim 17 which is

(*R,S*)-Ph-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*S*)-3-methoxyphenyl-CH(CH_2OH)CO-Pro-Pab(Z);

(*R*)-3-methoxyphenyl-CH(CH_2OH)CO-Pro-Pab(Z);

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OC(O)Et;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OC(O)Et; or

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-$OC(O)CH_3$;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-$OC(O)CH_3$;

[(*R,S*)-3-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab(Z); or

(*R,S*)-3-methylphenyl-CH(CH_2OAc)-C(O)-Pro-Pab-OMe;]

or a pharmaceutically acceptable salt thereof.

REMARKS

Reconsideration of this application is requested. Claims 1, 3-20, 28-30 and 32 are in the case.

I. THE 35 U.S.C. § 112, SECOND PARAGRAPH, REJECTION

Claims 17-19 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the reasons stated on page 3 of the Action. That rejection is respectfully traversed.

As pointed out in the response to the previous Office Action, claim 17 relates to compounds of formula Ia and not to compounds of formula I. While the compounds of formula Ia are related to the compounds of formula I (and hence share common definitions of certain groups), they differ from the compounds of formula I in that at least one H-atom in the terminal amidine group is replaced by OH, OR^a, $OC(O)R^b$, $OC(O)OR^c$, $C(O)OR^d$ or $C(O)R^e$. Thus, there is no overlap in terms of structure between the compounds of claim 1 and the compounds of claim 17. This is why claim 17 is independent of claim 1.

NO it is not

The reference in claim 17 to claim 1 does not create a dependency but, rather, is present as a way of obtaining concise claims (i.e.., of avoiding the repetition in claim 17 of definitions already provided in claim 1).

The independence of claim 17 from claim 1 is evident from the fact that the reference to claim 1 reads *"wherein…R^1, R^2, R^3, Y and n are as defined in claim 1"*. It is

quite clear from this wording that it is only the groups R^1, R^2, R^3, Y and n that are as defined in claim 1, and not the compounds of formula Ia.

Withdrawal of the outstanding 35 U.S.C. § 112, second paragraph, rejection is not believed to be in order. Such action is respectfully requested.

II. THE OBVIOUSNESS REJECTION

Claims 1, 3-13, 15-17, 19, 20, 28-30 and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 5,744,487 to Ohshima et al. The Examiner asserts that, because the compounds of current claim 1 fall within the generic disclosure of Ohshima, the skilled person would prepare those compounds in the expectation that they would be useful as thrombin inhibitors. The rejection is respectfully traversed.

In response, and without conceding to any merit in the rejection, claim 4 has been combined with claim 1 (i.e., the definition of R^1 has been amended to *"H"* alone). Claims 3 and 4 have been canceled without prejudice, *"(R,S)-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab"* has been canceled without prejudice from claim 10, and *"(R,S)-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab(Z)"* and *"(R,S)-3-methylphenyl-CH(CH_2OAc)-C(O)-Pro-Pab-OMe"* have been canceled without prejudice from claim 19.

Claim 1 as amended is clearly not rendered unpatentable by Ohshima. The number of compounds falling within the generic disclosure of Ohshima is vast. It is therefore completely implausible that the skilled person would make *every single one* of the compounds generically disclosed in that document simply on the basis that they *might* expect such compounds to have thrombin-inhibiting activity. On the contrary,

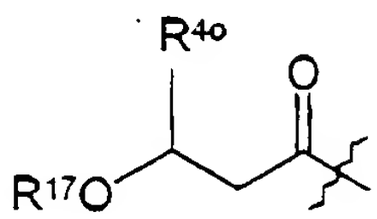
precisely because the generic disclosure of Ohshima covers so many compounds, the skilled person would not have prepared any given compounds falling within that generic disclosure in the absence of relevant motivation from the preferences and/or specific disclosures of Ohshima or another relevant prior art document.

The Examiner has failed to demonstrate the presence of the relevant motivation in the disclosure of Ohshima. No such motivation exists.

First, the preferences of Ohshima that relate to compounds in which R^4 represents OR^6 are all limited to compounds in which the group R^6 does not represent H (see column 5, lines 8-24, and column 6, lines 11-16 and 39-44). Further, the only area of overlap between the generic disclosure of Ohshima and claim 1 as amended is in respect of the compounds of Ohshima in which m represents 0. That is, when m represents 1, the group R^5 is present, and that group is always linked to the rest of the molecule *via* an O- or an N-atom. As the group –E-R^4 cannot represent H (see column 2, lines 1-31 of Ohshima), there is no way for the group –D-CH(R^5)-E-R^4 to represent HO-**CH_2**-R^x- as required by current claim 1.

The disclosure of Ohshima clearly indicates that compounds in which m is 1 are strongly preferred over all others (see column 6, lines 25 and 53, and column 7, lines 3 and 20). This is a clear teaching **away** from the present invention.

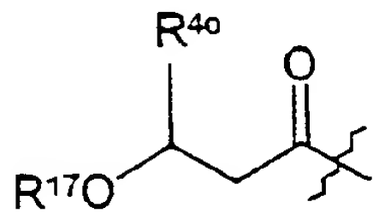
Finally, not one of the examples of Ohshima falls within the scope of claim 1 of the present case. Thus, there are no examples of Ohshima in which the group –D-(CHR^5)$_m$-E- represents C_2 alkylene when R^4 represents OR^6. Moreover, the only examples of Ohshima that contain a β-"OR"-substituted terminal acid group (compound numbers 341 and 372) can be represented by the following structure.



R^{17} is H and R^{4o} is ^{n}Bu or
R^{17} is C(O)OEt and R^{4o} is Ph

These are compounds of the generic disclosure of Ohshima in which m represents 1 (and R^5 represents OR^{17}).

By contrast, the most closely related compounds of current claim 1 can be represented by the following structure.



R^{17} is H and R^{4o} is ^{n}Bu or
R^{17} is C(O)OEt and R^{4o} is Ph

Ohshima does not provide any motivation to the skilled person to remove the β-"R^{4p}" group (to provide the compounds of current claim 1 in which "R^{4p}" represents H) or to move it to the α-position (to provide the compounds of current claim 1 in which "R^{4p}" represents phenyl, etc.)

Given the above, it is clear that the skilled person, when faced with the disclosure of Ohshima, would have had no motivation whatsoever to prepare a compound falling within the scope of claim 1 as presently amended. That claim, and all the claims that depend on or from it (i.e., claims 5-16, 20, 28-30 and 32), are therefore inventive over

Ohshima. Analogous arguments apply to the compounds of claim 17. That claim, and all claims dependent on or from it (i.e., claims 18, 19 and 31) are also inventive over Ohshima.

Ohshima does not give rise to a *prima facie* case of obviousness in the presently claimed invention. Reconsideration and withdrawal of the outstanding obviousness rejection are accordingly respectfully requested.

Allowance of the application is awaited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made.**"

Respectfully submitted,

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